SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

The undersigned wishes to thank Examiners Lezah Roberts, Ardin Marschel and Brian Kwon for the courtesy extended to him and to the CEO of the assignee, Dr. Gary Tollefson, in the personal interview of October 16, 2007.

Exhibits and/or Demonstrations

Clinical trial data of record were reviewed.

Identification of Claims Discussed

Claim 50.

Identification of Prior Art Discussed

O'Malley, US 6,004,970

Proposed Amendments

It was proposed that the claims be amended to define the amount of bupropion as an effective weight-loss amount and that the amount of naltrexone would be effective to enhance the action of bupropion, and to specify that both drugs are in a single dosage form.

Principal Arguments and Other Matters

O'Malley does not disclose combining the drugs in a single dosage form, and such combination would be contrary to the teaching of the reference. The data submission in the Cowley Declaration demonstrates unexpected results and overcomes any *prima facie* case.

Results of Interview

The PTO will reconsider the rejection in light of the showing of unexpected results upon submission of this response.

REMARKS

Claims 50-59 are amended. Claims 1-49 and 60-66 are canceled and Claims 54, 59 have been withdrawn. Claims 50-53 and 55-59 are thus presented for examination. The withdrawn claims should be rejoined upon allowance of the other independent claims.

Support for the amendments to Claim 50 are found, e.g., in Paragraphs **[0011], [0012], [0025], [0032]**, and **[0083],** as explained more fully below in connection with the discussion of those paragraphs. The 500 mg limitation in Claims 57 and 58 is supported, e.g., at paragraph **[0104]**. The remaining amendments are supported in the original claims and throughout the specification.

This amendment is accompanied by a RCE. This RCE withdraws finality of rejection, so that entry of this amendment is unquestionably proper. An IDS is also filed herewith to make of record the results of clinical weight-loss trials of bupropion and naltrexone monotherapy in the literature and to illustrate expectations in the art for weight loss drug combinations.

Rejection under 35 USC §103(a): Obviousness

Claims 50-53, 55-58, and 60-66 were rejected over a combination of references, with O'Malley as the primary reference. O'Malley discloses a method for smoking cessation through administration of an opioid receptor antagonist, including nalmefene. Nicotine can be coadministered. In addition, depending on clinical need, various other therapies can be administered, such as clonidine, acamprosate, serotonergic drugs, antihypertensives, antianxiety drugs, antidepressants, and sedatives. Wellbutrin (bupropion) is listed as one of the antidepressants that could be used. Routes of administration mentioned for the various drugs include IV, IM, intradermal, systemic, local, transdermal, oral, buccal, pulmonary, and parenteral.

The PTO argues that O'Malley differs from the claimed invention mainly in use of sustained release bupropion in the combination, and relies on secondary references for the proposition that sustained release drugs are known in the art and could be substituted into the combination of O'Malley. This characterization of O'Malley is respectfully traversed.

O'Malley does not disclose combining the drugs in a single dosage form

The claims, as amended, require that the naltrexone and bupropion are in a single oral dosage form. This is clearly different from what O'Malley discloses, and when taken with the knowledge in the art, O'Malley teaches away from this limitation.

The purpose of O'Malley's disclosure of administering the antidepressant is set forth in Col. 6, lines 1-6, as follows:

> In other embodiments, an opioid antagonist is administered in conjunction with an effective amount of an antidepressant or other agent known by the skilled worker to treat withdrawal, especially the depression associated with smoking cessation (such as Wellbutrin®, Paxil®, Sertraline®, Buspar®, Zofran®, or Prosac® [sic]).

It is respectfully submitted that antidepressant therapy is highly variable and should be customized for each patient. In order to treat depression, a physician will typically start with a lower dose of antidepressant and increase that dose (i.e., titrate the dose) to a level that works for that patient, e.g., 150-600 mg for bupropion. This would not be practical if the opioid antagonist and bupropion were in a single dosage form with fixed doses, for example 20 mg of naltrexone and 100 mg of bupropion. Giving more or less of that dosage form to adjust the amount of antidepressant would necessarily change the amount of opioid antagonist. In contrast to the presently-claimed invention, there is no disclosure in O'Malley that the two drugs are interacting cooperatively in the body, such that one enhances the action of the other. Instead, the antidepressant is used to treat withdrawal symptoms, "especially" depression, and the opioid is used to treat dependency. For this reason, the reference fails to establish *prima facie* obviousness and actually teaches away.

Even if there were a *prima facie* case, such a case must be reevaluated in light of all of the evidence when rebuttal evidence is submitted. Here, there has been a powerful showing of unexpected results in the Cowley Declaration submitted January 23, 2007. In evaluating that showing, it is important to consider what one of skill in the art would have understood regarding potential weight-loss effects of naltrexone and bupropion.

Expectations in the art for naltrexone and bupropion monotherapy

Despite some early evidence in animal models that naltrexone could cause weight loss, clinical studies indicate that it is a poor weight-loss drug in humans. Atkinson et al., *Clin Pharmacol Therap.* **38**:419-422 (1985) (8 weeks; 50 & 100 mg/day) ("Weight loss was not significant [for the whole group] compared with placebo," although women lost some while men did not); Malcolm et al., *Int. J. Obesity* **9**:347-353 (1985) (10 weeks; 200 mg/day) ("Naltrexone did not appear to have any significant beneficial weight reduction properties. . . . Naltrexone is of no value . . in the general treatment of obesity."); Mitchell et al., *Biol. Psychiatry* **22**:35-42 (1987) (11 weeks; 300 mg) ("Naltrexone is not superior to placebo.").

Bupropion, on the other hand, has exhibited weight loss properties in clinical trials. *See, e.g.*, Anderson et al., *Obesity Res.* **10:**633-641 (2002) (300 mg & 400 mg bupropion SR; 48 weeks, with diet and exercise) ("The weight losses at 48 weeks did not differ significantly from those at 24 weeks").

Thus, in light of the prior art, bupropion therapy would be expected to cause some weight loss for a period of time, e.g., up to 24 weeks, plateauing or rebounding thereafter, and naltrexone-induced weight loss would be expected to be insignificant.

Expectations in the art for combination therapy

The literature shows that the combination of two FDA approved weight loss drugs, sibutramine (MERIDIA) and orlistat (XENICAL), was not additive and that those who lost significant weight on sibutramine monotherapy did not lose more when orlistat was added to the regimen. (Wadden, et al, *Obesity Research* **8**(6):431 (2000)). The combination of two approved OTC weight loss drugs, phenylpropanolamine and benzocaine, showed no increase in weight loss. (Greenway et al., *Obesity Research* **7**(4):370-378 (1999)). Unapproved drugs caffeine and ephedrine, on the other hand, exhibit a synergistic thermogenic effect (Astrup et al., *Metabolism* **40**(3):323-329 (1991)), but adding the weight-regulating molecule leptin to that combination did not increase weight loss (Greenway et al., *Intl. J. Obesity* **26**(supp. 1):S136 (2002)). In contrast, the unapproved combination fen/phen provided enhanced weight loss, but with dangerous side effects. *See, e.g., Specification* at **¶[0005]**.

Thus, at the time the application was filed, it was unpredictable whether a combination of two weight-loss drugs would result in even an additive weight loss effect.

The claimed composition has unexpected properties for weight loss

The PTO has not, in this application, adequately addressed the unexpected results set forth in the Cowley Declaration. These results flow from carefully controlled clinical trials, conducted to FDA standards, and are statistically significant. The strength of these data go far beyond what is ordinarily required to overcome an obviousness rejection. When presented with such rebuttal evidence, the new **Section 103 Guidelines in view of KSR** reaffirm the established standard:

> Once the applicant has presented rebuttal evidence, Office personnel should reconsider any initial obviousness determination in view of the entire record. All the rejections of record and proposed rejections and their bases should be reviewed to confirm their continued viability. The Office action should clearly communicate the Office's findings and conclusions, articulating how the conclusions are supported by the findings.

In contrast to this requirement, the PTO's final Office Action did not address a single element of the data package in the declaration. No findings whatsoever were made relating to whether the results shown in the declaration were unexpected. Instead, the PTO merely reiterated the prior rejection and argued what the cited references teach, stating:

> Applicant's objective evidence or secondary consideration of showing unexpected results was carefully considered. However, the examiner finds that such evidence is not found persuasive. As discussed in the previous comments, the combination composition comprising naltrexone and bupropion, in any available dosage forms including sustained release forms (e.g., sustained release tablet) was well known at the time the invention was made.

This is not the type of reasoning required by KSR Guidelines or Section 2145 of the MPEP. The rejection is not an anticipation rejection. Contrary to the PTO's statement, no reference discloses all of the limitations of the claims. A composition and its properties are considered inseparable for purposes of obviousness. *In re Papesch,* 137 USPQ 43 (CCPA 1963). Unless the properties are expected and obvious, the composition is not obvious.

The documented unexpected properties mandate withdrawal of the rejection

The "composition-and-its-properties" principle from *In re Papesch* was recently reaffirmed by the Federal Circuit in the post-KSR decision, *In re Sullivan,* 2007 U.S. App. LEXIS 20600 (Fed. Cir. 2007). In that case, involving composition claims, the Federal Circuit chastised the Examiner and the Board for ignoring evidence of record relating to the unexpected properties of the composition, holding instead that:

> The issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use. That unexpected property is relevant, and thus the declarations describing it should have been considered by the Board.

Similarly, in this case, the declaration describing the unexpected property should be considered by the PTO. Unless it can be established that the properties of the composition are expected, the rejection must be withdrawn.

As agreed in the interview, the claims have now been amended to specify effective amounts and roles for each compound. Thus, bupropion is used as a weight loss drug and its effects are enhanced by naltrexone, both in amounts effective for this cooperative result. This cooperative result (one drug enhancing the other), seen in the data of record, is different from the effect one of skill in the art would expect from merely administering two weight loss drugs together.

Naltrexone's ability to enhance the weight loss properties of bupropion was unknown prior to the present invention. With reference to particular paragraphs in the specification, (and without being bound to a particular theory of operation), the postulated mechanism for this enhancement is as follows. A dopamine/norepinephrine reuptake inhibitor (e.g., bupropion) can stimulate POMC neurons to release α-MSH which stimulates MC4-R, causing weight loss through decreased food intake and increased energy expenditure. *Specification* at ¶¶ **[0011], [0025], [0031]**. However, when POMC neurons release α-MSH, they also release β-endorphin, an agonist of the mu-opioid receptor on POMC, which downregulates α-MSH release in an autofeedback mechanism. *Id.* at **¶[0012]** This autofeedback mechanism is believed to explain why drugs such as bupropion lose their effectiveness as weight loss agents after several weeks. Naltrexone is an antagonist for the mu-opioid receptor, and blocks this feedback mechanism, resulting in continued release of α-MSH. *Id.* at **¶¶[0012], [0021]**. Thus, bupropion stimulates α-

MSH release with resultant weight loss, and naltrexone enhances that effect by inhibiting the autofeedback mechanism that would otherwise decrease bupropion's effectiveness.

Because the claimed composition produces unexpected results as a result of cooperative biological interactions between bupropion and naltrexone, and because the claims now specify effective amounts to achieve that cooperative result, it is believed that all basis for an obviousness rejection has been removed. Accordingly, prompt allowance of this application is respectfully requested.

No Disclaimers or Disavowals

Although the present communication includes amendments to the claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following continuing applications.

Serial Number	Title	Filed
11/356,839	Compositions for Affecting Weight Loss	02/17/2006
11/779,008	Compositions for Affecting Weight Loss	07/17/2007
11/778,873	Compositions for Affecting Weight Loss	07/17/2007

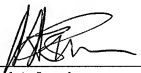
Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

In light of the foregoing, it is believed that the application is in condition for allowance. If any issues remain, the Examiner is invited to contact the undersigned by telephone to resolve them, thus facilitating a prompt allowance.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10-19-07

By: 

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